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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,316	03/29/2004	Chandra U. Singh	AZAY:006US	1828

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EXAMINER	
MAIER, LEIGH C	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
05/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,316	SINGH ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-13,20 and 22-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13,20 and 22-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 7, 2008 has been entered.

Claim 21 has been canceled. Claim 2 has been amended. Claim 31 is newly added. Claims 2-13, 20 and 22-31 are pending. Any rejection or objection not expressly repeated has been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 2, 3, 5-8, 13, 20-22 and 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braude et al (WO 00/47215) and Pitha (US 4,727,064).

Claim 2 has been amended to include a weight ratio for the digitalis glycoside to cyclodextrin of 1:100 to 1:20.

Braude teaches the administration of cardiac glycosides (CGs) for the treatment of a variety of tumors. See abstract and pages 7-12. The most preferred compounds include CGs such as digoxin, ouabain and oleandrin. See page 15 at first paragraph. The reference further suggests these agents in combination with a variety of typical excipients, such as preservatives and

buffers. See page 18. The reference further teaches dosages and methods of administration. See page 19.

Pitha discloses the preparation of inclusion complexes comprising an amorphous CD and CGs, digoxin and oubain. The CG:CD weight ratio of these compositions is about 1:10 and about 1:5, respectively. The reference exemplifies other drug:CD compositions having a weight ratio within the recited range. The complexes are freeze-dried and compressed into tablets with a cellulose excipient. See abstract; Table 1; and examples 4-6. The solubility of the exemplified CGs is greatly enhanced by complexation with the CD. The compositions listed in Table 1 comprise either 40% or 50% of the HPCD. The reference further suggests the preparation of compositions comprising higher concentrations, up to 95%, of the CD. See col 2, lines 62-65.

It would have been obvious to one having ordinary skill in the art at the time the invention was known to modify the method of Braude—treatment of tumors with CGs—by preparing CD complexes, as taught by Pitha, to enhance their solubility. Pitha demonstrated the dramatically increased solubility of CGs—digoxin, for example. The steroidal moiety—that is, the hydrophobic portion of the molecule that interacts with a cyclodextrin in complexation—of oleandrin differs from that of digoxin by the mere addition of an acetyl group. Because of this great similarity in structure, one of ordinary skill would reasonably expect success in preparing such complexes of the recited compounds and administering them for the treatment of cancer, a proliferative disease. In the absence of unexpected results, it would be within the scope to prepare compositions of an appropriate concentration for administration to a patient at the necessary dosage as determined by routine experimentation. It would be further within the scope of the artisan to administer the complex to the patient by any appropriate means. With respect to

amended claim 13, it would be further obvious to prepare a composition comprising oleandrin and a cyclodextrin and further comprising another of the recited CGs for the treatment of cancer. One of ordinary skill would be motivated to prepare this combination for the additive effect.

With respect to the new limitation regarding the weight ratio, the reference exemplifies drug:CD compositions having a weight ratio within the recited range. It also suggests the preparation of compositions having very high concentrations of CD. In the absence of unexpected results, it would be within the scope of the artisan to optimize the ratio of these components for their administration for the treatment of disease through routine experimentation. Applicant has demonstrated no criticality for this weight ratio range.

Applicant's arguments filed March 7, 2008 have been fully considered but they are not persuasive. Applicant again argues the cited references in a piecemeal fashion. This was addressed in the previous Office action. Applicant further argues that the rejection is moot in light of the amendment to claim 2. This is not found persuasive as discussed above.

Claims 2-8, 13, 20-22 and 24-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braude et al (WO 00/47215) and Pitha (US 4,727,064) in view of Jones (US 4,555,504).

Braude and Pitha teach as set forth above. The references do not teach the use of an antioxidant.

Jones teaches the preparation of inclusion complexes comprising a CD and cardiac CGs, such as digoxin. These complexes are isolated by lyophillization (freeze-drying). See examples 1, 2 and 6. The reference further teaches that CGs, generically, form complexes with CDs,

affording a much greater solubility of these compounds. See col 1, lines 42-53. The reference teaches molar ratios (CD:CG) of 10:1 to 1:10. See col 2, lines 35-42. The weight ratios would be about 15:1 to 1:15 for digoxin and β–CD, for example. In using HPCD, as taught by Pitha, the weight ratios would be about 20:1 to 1:20. The reference further teaches the inclusion of typical pharmaceutical additives, such as buffers, antioxidant, binders and preservatives. See col 3, lines 58-65.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the CD:CG complexes, as discussed above with the further addition of an antioxidant because Jones had taught its utility in such compositions. Jones further supports the idea that CGs, generically are suitable for complexation with CDs for enhanced solubility. In the absence of unexpected results, one of ordinary skill would reasonably expect success in preparing such a composition for the treatment of cancer. As above, it the absence of unexpected results, it would be within the scope of the artisan to optimize the ratio of these components for their administration for the treatment of disease through routine experimentation.

Applicant's arguments filed March 7, 2008 have been fully considered but they are not persuasive. It appears to be Applicant's position that it is invalid to rely on Jones for a teaching regarding weight ratios because Jones does not teach the treatment of cancer. This is not considered persuasive. It is Braude that teaches the treatment of cancer, as discussed above. Jones teaches a CD:CG composition that is suitable for administration for the treatment of disease. In the absence of unexpected results, one of ordinary skill, knowing that a drug has utility for the treatment of both A and B, would select a particular *composition* of that drug to treat either of these diseases with a reasonable expectation of success. The treatment of A may

differ from the treatment of B in dosage amounts, protocol, etc., but in the absence of a demonstrated criticality, one of ordinary skill would reasonably expect success in using the composition made obvious by this combination of references as the vehicle for the administration of the drug.

Claims 2-11, 13, 20-22 and 24-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braude et al (WO 00/47215) and Pitha (US 4,727,064) in view of Jones (US 4,555,504) and Stella et al (US 5,874,418).

Braude, Pitha and Jones teach as set forth. The combination of references does not teach the full scope of additives and excipients recited in the claims.

The recited additives and excipients are common and well known in the art. See, for example Stella at col 19-20.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the compositions as set forth above. In the absence of unexpected results, it would be within the scope of the artisan to further modify them by the addition of any common additives or excipients known in the art. The examiner finds no criticality in any recited excipient or weight ratio.

Applicant presents no new argument with respect to this rejection.

Claims 2, 3, 5-8, 13 and 20-30 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Braude et al (WO 00/47215) and Pitha (US 4,727,064) in view of Rubinfeld et al (US 5,824,668).

Braude and Pitha teach as set forth. The combination of references does not teach the sterilization of such a composition by filtration.

Sterilization of a solution by filtration is well known in the art. Rubinfeld teaches specifically that a solution comprising a cyclodextrin complex may be sterilized by filtration through a 0.2 micron filter and generally discusses the importance of purity and sterility in pharmaceutical products. See col 11, lines 25-58.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to sterilize a solution comprising a solution comprising a CG/CD complex by filtration. Preparation of sterile solutions for distribution and administration to human subjects is the standard of care in the pharmaceutical industry. It would be within the scope of the artisan to select any method, such as filtration, with a reasonable expectation of success.

Applicant presents no new argument with respect to this rejection.

Claims 2, 3, 5-8, 12-22 and 24-30 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Braude et al (WO 00/47215) and Pitha (US 4,727,064) and further in view of either of (1) Sasaki et al (US 4,454,315); (2) Larm et al (US 4,707,471); (3) Williams et al (US 4,833,131); (4) Kanamaru et al (US 5,135,920) or (5) Raz et al (US 5,895,784).

Braude and Pitha teach as set forth above. The combination of references does not teach the use of the polysaccharides recited in claim 12.

The polysaccharides recited in claim 12 are all known for the use in the treatment of cancer. See, for example, (1) Sasaki at abstract; (2) Larm at col 4; (3) Williams at abstract; (4) Kanamaru at abstract or (5) Raz at abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the composition made obvious by Braude and Pitha for the treatment of cancer. In the absence of unexpected results, it would be further obvious to combine any other agent known to be effective in treating cancer, such as those recited in claim 12, for the additive effects.

Applicant's arguments filed March 7, 2008 have been fully considered but they are not persuasive.

Applicant again professes an inability "to identify any teachings there [in (1) Sasaki; (2) Larm; (3) Williams; (4) Kanamaru; or (5) Raz] relevant to oleandrin/cyclodextrin combinations and their use in cancer treatment." As clearly stated above, Braude and Pitha teach the combination of oleandrin and CD for the treatment of cancer. It is settled law that it is prima facie obvious to combine components that are known to have the same utility for the expected additive effect. Given that the tertiary references teach that the recited polysaccharides have utility in the treatment of cancer, their addition to another composition, also known to have utility in the treatment of cancer, would be obvious, as set forth in the previous Office action.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Monday, Wednesday and Thursday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Anna Jiang (571) 272-0627, may be contacted. The fax number for Group 1600, Art Unit 1623 is (571) 273-8300.

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/Leigh C. Maier/
Primary Examiner, Art Unit 1623
May 7, 2008